

Severe Viral Infections and Primary Immunodeficiencies

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Patients with severe viral infections are often not thoroughly evaluated for immunodeficiencies. In this review, we summarize primary immunodeficiencies that predispose individuals to severe viral infections. Some immunodeficiencies enhance susceptibility to disease with a specific virus or family of viruses, whereas others predispose to diseases with multiple viruses in addition to disease with other microbes. Although the role of cytotoxic T cells in controlling viral infections is well known, a number of immunodeficiencies that predispose to severe viral diseases have recently been ascribed to defects in the Toll-like receptor–interferon signaling pathway. These immunodeficiencies are rare, but it is important to identify them both for prognostic information and for genetic counseling. Undoubtedly, additional mutations in proteins in the innate and adaptive arms of the immune system will be identified in the future, which will reveal the importance of these proteins in controlling infections caused by viruses and other pathogens.

The majority of viral infections acquired by nonimmunosuppressed individuals are asymptomatic or result in mild clinical manifestations. These individuals are able to mount effective immune responses that either clear the virus from the body or, for viruses that establish latency, maintain the virus in a dormant state. For individuals who are immunocompromised, because of a genetic immunodeficiency or immunosuppressive drug therapy, viral infections may result in life-threatening disease. Such patients present with infections that are severe, persistent, recurrent, or refractory to therapy and are usually caused by viruses of low virulence prevalent in the community.

In this review, we discuss primary immunodeficiencies that predispose individuals to severe viral infections in the presence or absence of an increased susceptibility to severe disease with other pathogens. Primary immunodeficiency disorders can be divided into 2 broad categories: disorders caused by defects in the innate immune system (Toll-like receptors [TLRs], interferons [IFNs], natural killer [NK] cells) and those caused by defects in the adaptive immune system (lymphocyte-derived cellular and antibody responses). In the past, susceptibility to severe viral diseases has usually been attributed to deficient lymphocyte responses, especially CD8⁺ T-cell responses. However, susceptibility to severe viral diseases is encountered in primary immunodeficiency disorders with deficient innate and/or adaptive immune responses. Recently, primary immunodeficiencies due to mutations in signaling proteins in the innate immune system have been described [1]. Some of these mutations predispose individuals to severe pathogen-specific diseases; thus, despite the importance of these pathways for the control of multiple pathogens, individual cellular proteins can be important for the control of individual pathogens.

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PRIMARY IMMUNODEFICIENCIES WITH A UNIQUE PREDISPOSITION TO A PARTICULAR VIRAL DISEASE

Primary Immunodeficiencies Associated With Severe Epstein-Barr Virus Infection

X-linked lymphoproliferative (XLP) syndrome, or Duncan's disease, is characterized by fulminant infectious mononucleosis and/or hemophagocytic lymphohistiocytosis (HLH) that results from failure to control the proliferation of activated T cells and NK cells that arise after Epstein-Barr virus (EBV) infection (Table 1). If not treated, this frequently progresses to fatal lymphoproliferative disease. Patients with XLP syndrome are usually healthy until they are infected with EBV; however, some patients develop B cell lymphomas, vasculitis, or lymphomatoid granulomatosis in the absence of EBV infection.

Two genetic causes of XLP syndrome have been identified. Mutations in signaling lymphocyte activation molecule (SLAM)-associated protein cause XLP-1 and prevent inhibition of signal transduction by SLAM, so that the proliferation of T cells and NK cells continues unchecked with infiltration of organs by these cells [2, 3]. Mutations in X-linked inhibitor of apoptosis cause XLP-2 and predispose to EBV-associated HLH in 90% of affected individuals [4]. Some investigators have suggested that this disease be reclassified as X-linked HLH, because of the high prevalence of HLH, and no patients with lymphoma have been reported [5]. Rituximab has been successful in treating a few patients with XLP-1 and fulminant mononucleosis, but it has not been proved effective in clinical trials [6]. Treatment may include HLH therapy [7], which includes etoposide and corticosteroids. Hematopoietic stem cell transplantation is curative for XLP-1 [8].

A mutation in interleukin (IL)-2-inducible T-cell kinase was reported to cause severe EBV-associated lymphoproliferative syndrome in 2 sisters who developed fatal disease with hepatosplenomegaly and hepatic dysfunction; 1 developed B cell lymphoma [9]. Patients with mutations in SLAM-associated protein and IL-2 inducible T-cell kinase have a lack or absence of NK T (NKT) cells, suggesting a probable role for this rare population of lymphocytes in controlling EBV infection.

Chronic active EBV infection is another condition that may result in a severe or fatal lymphoproliferative syndrome. The syndrome is characterized by a progressive EBV-positive lymphoproliferative disease, usually after primary EBV infection, with lymphadenopathy, splenomegaly, liver dysfunction, and often hemophagocytosis. Patients have markedly elevated EBV viral loads in the blood and often develop EBV-positive lymphomas. One patient was described with mutations in both copies of the perforin gene and impaired T-cell killing [10].

Primary Immunodeficiencies That Predispose to Herpes Simplex Virus 1 Encephalitis

IFNs possess a critical role in defense against viral infections. Production of type I IFNs (α and β) by virus-infected leukocytes, fibroblasts, or epithelial cells is induced by the binding of viral glycoproteins or RNA/DNA to membrane-bound TLRs or cytoplasmic receptors (eg, retinoic acid-inducible gene 1) (Figure 1) [11]. These interactions recruit signaling molecules and trigger a cascade of events that produce type I IFNs. In turn, these IFNs bind to receptors and activate other signaling molecules that turn on the expression of IFN-stimulated genes and the antiviral response. TLRs have additional effects on the innate immune response, and they recruit and ultimately lead to activation of antigen-specific B and T cells.

Mutations in 3 proteins in the TLR signaling pathway have been linked to herpes simplex encephalitis (HSE) in children. Two children were reported with autosomal recessive homozygous mutations in UNC-93 homolog B1 (UNC93B1) that caused impaired activity of the protein (Table 1) [12]. UNC93B is essential for trafficking of TLR7 and TLR9 from the endoplasmic reticulum (ER) to the endosome and for TLR3, TLR7, TLR8, and TLR9 signaling [13]. The 2 children had recurrent encephalitis that responded to acyclovir but no other symptoms related to herpes simplex virus (HSV) or other viral diseases. The second identified genetic cause of isolated HSE was an heterozygous, autosomal dominant mutation in TLR3 that functioned in a dominant-negative fashion to impair TLR3 activity [14]. The 2 patients presented at ages 5 months and 5 years. One of them had recurrent encephalitis that responded to acyclovir. Interestingly, several family members with the same heterozygous mutation in TLR3 have had no clinical manifestations, indicating that the clinical penetrance of this defect for HSE is incomplete.

An autosomal dominant-negative mutation in tumor necrosis factor receptor-associated factor 3 (TRAF3) was identified in a child who presented at 4 years of age with HSE and recovered [15]. TRAF3 functions downstream of UNC93B and TLR3 in the cytoplasm and leads to production of type I IFNs (Figure 1). The evidence suggests that impaired TLR3 signaling via the UNC93B- or TRAF3-dependent pathway is essential for protective immunity to HSV-1 in the central nervous system during the course of primary infection in some children. None of the children with defects in these TLR signaling pathways had other severe viral infections. Most children with a single episode of HSE or recurrent HSE still have no identified genetic cause. However, the fact that mutations in 3 proteins in the IFN signaling pathway predispose to HSE suggests that additional proteins in this pathway may be responsible for other cases of HSE. Prompt treatment with intravenous acyclovir is important, and addition of IFN- α has been proposed.

Primary Immunodeficiencies That Predispose to Severe Human Papillomavirus Infection

Epidermodysplasia verruciformis is a rare autosomal recessive genodermatosis in which patients develop warts on the dorsum of the extremities and pityriasis versicolor-like lesions on the trunk, neck, and face; lesions in sun-exposed areas often become malignant later in life. Lesions are caused by human papillomavirus (HPV) serotypes that are ubiquitous and nonpathogenic in normal populations (Table 1) [16]; they do not regress and are usually refractory to standard therapy, IFN- α , and retinoids. Homozygous mutations in *EVER1* and *EVER2*, adjacent genes on chromosome 17, have been identified in 75% of patients with this condition [17, 18]. The proteins encoded by these genes are membrane proteins in the ER and are predicted to form channels; their function is unknown.

WHIM syndrome, manifested by warts, hypogammaglobulinemia, infections, and myelokathexis (retention of neutrophils in the bone marrow), is a rare autosomal dominant genetic disease caused by mutations in the chemokine receptor gene, *CXCR4* (Table 1) [19]. This syndrome predisposes individuals to disseminated, chronic, and treatment-refractory warts. In addition, the syndrome is characterized by moderate to severe neutropenia and recurrent sinopulmonary bacterial infections. *CXCR4* and its ligand, *CXCL12*, are important for lymphocyte trafficking, release of neutrophils from the bone marrow, and bone marrow homeostasis. Recent data reveal that patients with WHIM syndrome have a paucity of dendritic cells and an impaired capacity to produce IFN- α in response to viral stimulation [20].

Primary Immunodeficiencies That Predispose to Severe Enterovirus Infection

X-linked agammaglobulinemia (XLA or Bruton's agammaglobulinemia) is caused by failure of B-cell development due to a mutation in the *BTX* gene that encodes Bruton's tyrosine kinase (Table 1). Patients usually present between 3 and 18 months of age with poor growth, failure to thrive, and chronic diarrhea. Since patients have agammaglobulinemia or severe hypogammaglobulinemia, they have recurrent bacterial infections, leading to respiratory tract infections, sepsis, osteomyelitis, and meningitis. However, patients with XLA also exhibit an increased susceptibility to infection with enteroviruses (eg, echovirus, poliovirus, coxsackievirus). The most common disease manifestation is chronic meningoencephalitis; hepatitis and dermatomyositis can occur. Patients with XLA can develop poliomyelitis after receiving the live attenuated oral polio vaccine or coming in close contact with a recipient of this vaccine. Patients with autosomal recessive agammaglobulinemia and common variable immunodeficiency are also at increased risk of severe enterovirus infection. Enterovirus infections in these patients are often systemic and chronic and

usually fatal. In a study of 201 patients with XLA, the most common cause of death was a chronic enterovirus infection [21]. Other viral infections described in these patients included rotavirus, adenovirus, and hepatitis C virus. Intravenous, and in some cases, intrathecal immunoglobulin (for meningoencephalitis) has been used for treatment. The susceptibility of these patients to severe enterovirus infections reveals the importance of antibody neutralization for controlling these infections.

Primary Immunodeficiency Predisposing to Kaposi Sarcoma

A 2-year-old child born to consanguineous parents developed rapidly progressive, disseminated, fatal Kaposi sarcoma and was found to have a homozygous mutation in stromal interaction molecule 1 (STIM1) [22]. Except for infection with human herpesvirus 8, the child did not have a history of other severe infections. STIM1 is an ER resident transmembrane protein that senses the depletion of ER calcium stores. Two patients with immunodeficiency, opportunistic infections (cytomegalovirus [CMV], varicella zoster virus [VZV]), and autoimmunity were previously reported to have mutations in STIM1 [23].

PRIMARY IMMUNODEFICIENCIES WITH A PREDISPOSITION TO SEVERE DISEASE ASSOCIATED WITH MULTIPLE VIRUSES AND OTHER MICROBES

Immunodeficiencies Due to Impaired Killing by Cytotoxic T Cells and Natural Killer Cells

Cytotoxic T cells and NK cells kill cells by releasing granules that enter target cells and induce apoptosis (Figure 2). Familial HLH, an autosomal recessive disorder, is caused by a deficiency in 1 of 4 proteins involved in NK and T-cell killing (Table 2) [24]. Perforin, munc 13-4, syntaxin 11, and syntaxin-binding protein 2 are important for secretion of cytotoxic granules from NK or cytotoxic T cells or for entry of these granules into virus-infected cells. Familial HLH has frequently been reported to be triggered by EBV, although other viruses (eg, CMV, VZV, HSV, parvovirus B19, adenovirus) and pathogens (eg, bacteria, fungi, parasites) have been implicated. The inability to destroy virus-infected cells causes a persistent, uncontrolled activation of T cells and macrophages with overproduction of inflammatory cytokines and hemophagocytosis. Patients develop liver disease and bone marrow failure which is fatal unless treated. The HLH-2004 protocol, which includes dexamethasone, etoposide, and cyclosporine, can result in remissions; hematopoietic stem cell transplantation is curative [25].

Three types of NK-cell deficiency syndromes have been described: absolute (absence of NK and NKT cells), classic (absence of NK cells), and functional (impaired NK-cell activity) (Table 2) [26]. NK cells are the primary cytolytic lymphocytes of the innate immune system. One patient with absolute NK-cell deficiency experienced disseminated varicella with pneumonia,

Table 1. Primary Immunodeficiencies Predisposing to Specific Viral Diseases

Viral infection or disease and references	Mutated gene(s)/protein	Immunodeficiency or syndrome	Disease-specific history	Key clinical manifestations	Key immunologic findings
EBV					
Coffey et al [2], Sayos et al [3]	<i>SH2D1A</i> /signaling lymphocyte activation molecule-associated protein	XLP syndrome 1	History of death due to EBV infection in male relatives on maternal side; XLP syndrome may develop in the absence of EBV infection	Fulminant infectious mononucleosis; HLH; B cell lymphoma; vasculitis; pulmonary lymphomatoid granulomatosis ^a	Normal B- and T-cell counts; impaired T- and NK-cell killing; low or absent NKT cells ^b ; dysgammaglobulinemia (decreased IgG1 or IgG3; increased IgA or IgM); impaired antibody responses to infection and vaccination
Rigaud et al [4], Marsh et al [5]	<i>BIRC4</i> /X-linked inhibitor of apoptosis	XLP syndrome 2	History of death due to EBV infection in male relatives on maternal side	Fulminant infectious mononucleosis; HLH; splenomegaly; hepatitis	NK lymphopenia; reduced survival of NK cells; normal or low NKT cell counts; increased apoptosis of T cells; hypogammaglobulinemia
Huck et al [9]	<i>Itk</i> /interleukin-2 inducible T-cell kinase	EBV-associated lymphoproliferative syndrome	Unknown	Recurrent fever; cytopenias; lymphadenopathy; hepatosplenomegaly; lymphoma	Moderately decreased T-cell counts; absent NKT cells; normal or decreased serum immunoglobulin levels
Katano et al [10]	<i>PRF1</i> /perforin 1	Chronic active EBV infection	Severe progressive illness that began after primary EBV infection; no family history	Prolonged fever; lymphadenopathy; hepatosplenomegaly; HLH (occasionally); lymphoma	Progressive cellular and humoral immunodeficiency; hypogammaglobulinemia; with or without decreased NK-cell activity and decreased cytotoxic T-lymphocyte activity
Herpes simplex virus 1 (encephalitis)					
Casrouge et al [12]	<i>UNC93B1</i> /UNC93B1 protein	UNC93B deficiency	Sporadic, possibly recurrent encephalitis	Childhood HSE; otherwise healthy	Lack of TLR3, TLR7, TLR8, TLR9 signaling; impaired cellular responses to IFN- α/β and - λ
Zhang et al [14]	<i>TLR3</i> /TLR3	TLR3 deficiency	Sporadic, possibly recurrent encephalitis	Childhood HSE; otherwise healthy	Impaired TLR3 signaling; impaired TLR3-dependent induction of IFN- α , - β , and - λ
Perez de Diego et al [15]	<i>TRAF3</i> /TRAF 3	TRAF3 adaptor molecule deficiency	Sporadic encephalitis	Childhood HSE; otherwise healthy	Impaired TLR3-dependent induction of type I IFN and IFN- λ
Human papillomavirus					
Ramoz et al [17], McDermott et al [18]	<i>EVER1</i> , <i>EVER2</i> /epidermodysplasia verruciformis 1 and 2	Epidermodysplasia verruciformis	Malignant transformation of warts in 30%–70% of patients	Disseminated warts: flat or macular hypo- or hyperpigmented lesions resembling pityriasis versicolor	With or without decreased T-lymphocyte counts and decreased T-cell responsiveness to mitogens; decreased cell-mediated immunity based on nonspecific in vitro and in vivo tests

Table 1 continued.

Viral infection or disease and references	Mutated gene(s)/protein	Immunodeficiency or syndrome	Disease-specific history	Key clinical manifestations	Key immunologic findings
Hernandez et al [19]	<i>CXCR4</i> /chemokine receptor 4	WHIM syndrome	Recurrent sinopulmonary bacterial infections; chronic cutaneous and genital warts	Neutropenia (neutrophil count <500 cells/ μ L)	With or without decreased IgG and IgA but normal IgM levels; normal antibody responses to vaccination; normal T-lymphocyte subsets; possible impairment of in vitro responses to mitogens and antigens; cutaneous anergy to recall antigens
Enterovirus Winkelstein et al [21]	<i>BTK</i> /Bruton's tyrosine kinase	X-linked agammaglobulinemia	Affected male family members; recurrent sinopulmonary infections with encapsulated bacteria; chronic enteroviral meningoencephalitis; <i>Flexispira</i> / <i>Helicobacter</i> intravascular/lymphatic infection; <i>Salmonella</i> / <i>Campylobacter</i> gastroenteritis	Absent tonsils and adenoids; palpable lymph nodes are absent; hepatosplenomegaly; complete absence of hair or eyebrows; severe eczema; oral thrush; <i>Candida</i> skin infections	Profound hypogammaglobulinemia; agammaglobulinemia; absent or very low B cell numbers; absence of specific antibody responses; normal T-cell counts and function
Human herpesvirus 8 Byun et al [22]	<i>STIM1</i> /stromal interaction molecule 1	Classic Kaposi sarcoma in childhood	Rapidly disseminated disease; lymphadenopathy; hepatosplenomegaly; pulmonary lesions	Autoimmune hemolytic anemia; human immunodeficiency virus negative	Normal T-, B-, and NK-cell counts and subsets; normal immunoglobulin levels

Abbreviations: EBV, Epstein-Barr virus HLH, hemophagocytic lymphohistiocytosis; HSE, herpes simplex encephalitis; IFN, interferon; Ig, immunoglobulin; NK, natural killer; NKT, natural killer T; TLR, Toll-like receptor; TRAF3, tumor necrosis factor receptor-associated factor 3; UNC93B1, UNC-93 homolog B1; WHIM syndrome, syndrome manifested by warts, hypogammaglobulinemia, infections, and myelokathexis; XLP, X-linked lymphoproliferative.

^a Aplastic anemia and lymphocytic vasculitis are rare manifestations.

^b NKT cells include CD3⁺, CD56⁺, and CD16⁺ T cells, which recognize intracellular pathogens in the presence of CD1 and kill virus-infected cells.

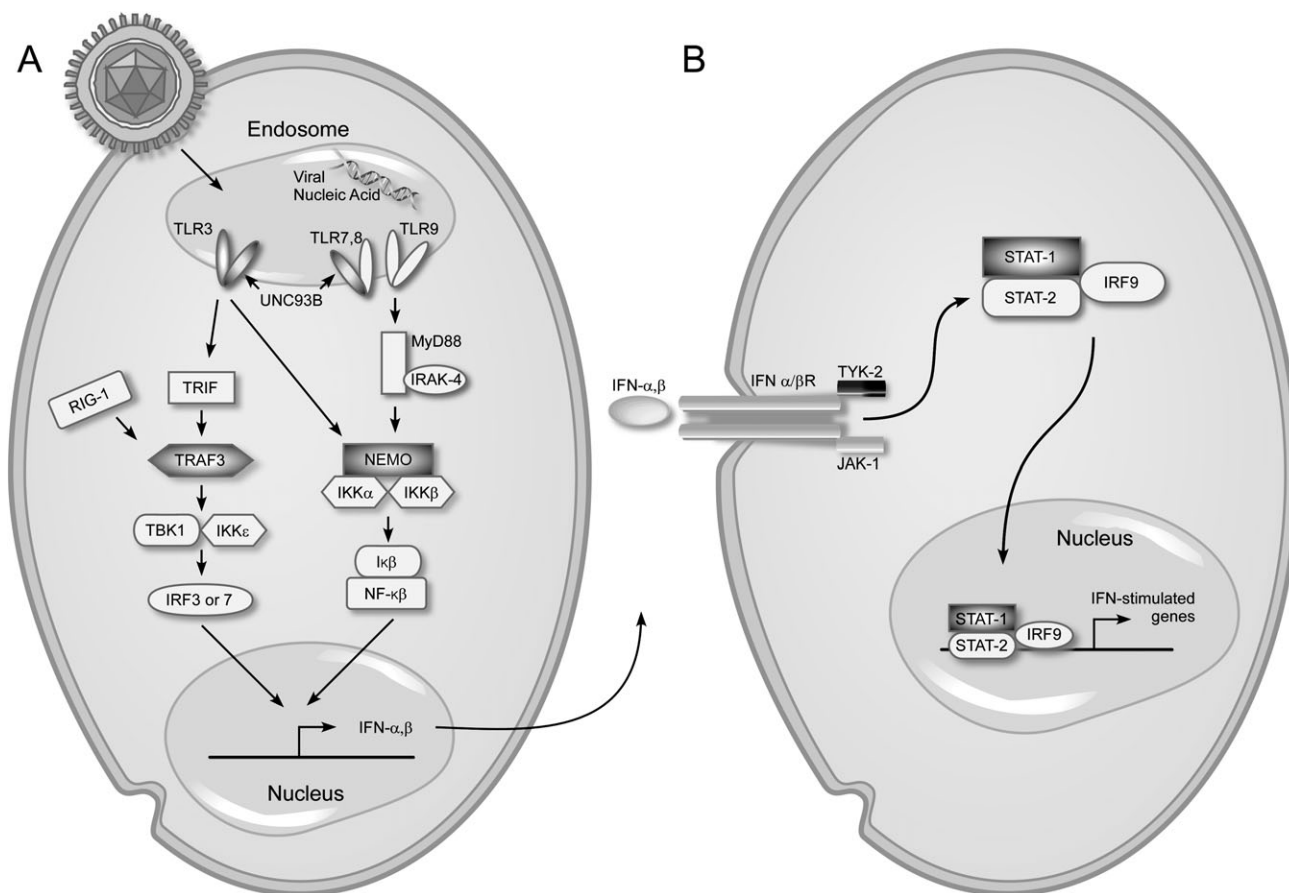


Figure 1. Toll-like receptor (TLR) and type I interferon (IFN) signaling pathways. *A*, Induction of type I IFN production in cells. Viral nucleic acids are detected by TLRs 3, 7, 8, and 9. TLR3 activation results in signaling through the Toll–interleukin (IL)–1R domain–containing adapter–inducing IFN- β (TRIF)–dependent or nuclear factor (NF)– κ B essential modulator (NEMO)–dependent pathway. Activation of TLRs 7, 8, and 9 results in signaling through the myeloid differentiation factor 88 (MyD88)–dependent pathway. Transcription factors, IFN regulatory factor (IRF) 3, IRF7, or NF- κ B, initiate transcription of IFN genes in the nucleus. IKK, inhibitor of NF- κ B kinase subunit alpha or beta; I κ B, inhibitor of κ B; IRAK-4, IL-1R–associated kinase; RIG-1, retinoic acid–inducible gene 1; TRAF3, tumor necrosis factor receptor–associated factor 3; TBK1, TANK-binding kinase 1. RIG 1 is a cytosolic virus sensor. *B*, Response of cells to IFN. IFNs bind to the IFN receptor and initiate signaling through the signal transducer and activator of transcription (STAT) pathway to induce transcription of IFN-stimulated genes that inhibit viral replication. Mutations in shaded genes have been associated with severe HSV infections, including herpes simplex encephalitis (HSE). Mutations in TYK-2, tyrosine kinase 2, have not been associated with HSE.

CMV pneumonia, and disseminated HSV [27]. Patients with classic NK-cell deficiency can present with severe HPV infection [28]. Functional NK-cell deficiency is the most common and can present with severe invasive herpesvirus infections. Mutations in CD16 (encoded by the Fc gamma receptor IIIa gene) are the only mutations linked with an NK-cell deficiency to date [29]. CD16 is an Fc receptor expressed on the vast majority of NK cells that facilitates antibody-mediated cellular cytotoxicity and is involved in the lysis of virus-infected cells, independent of antibody binding. NK-cell deficiencies are also part of rare immunodeficiency syndromes, such as Wiskott-Aldrich syndrome [30].

Immunodeficiencies Resulting From Defects in the Interferon Pathway

Immunodeficiencies involving the IFN pathway include those that affect the production of IFN (eg, nuclear factor [NF]– κ B

signaling) and those that affect the response of cells to IFN (IFN receptor and signaling molecule mutations) (Figure 1). These immunodeficiencies predispose individuals to infection with intracellular pathogens, such as viruses, mycobacteria, and salmonella [31].

X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency results from mutations in inhibitor of NF- κ B kinase γ , also known as NEMO (NF- κ B essential modulator). In addition to abnormalities in sweat glands and teeth, mutations in this protein predispose individuals to infections with viruses and bacteria (Table 2) [32]. The viral infections in these patients have been caused primarily by herpesviruses (eg, CMV sepsis and colitis; HSV stomatitis, pharyngitis, and encephalitis) (Table 2) [33, 34].

Homozygous or heterozygous dominant-negative mutations in IFN- γ receptors 1 or 2 predispose individuals primarily to

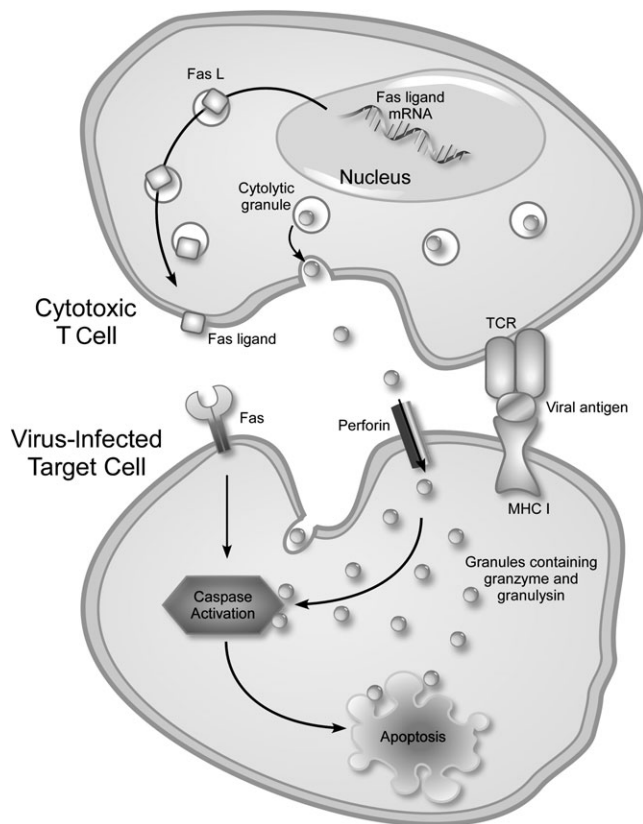


Figure 2. Killing of virus-infected target cells by cytotoxic T cells. Cytotoxic T cells recognize virus-infected target cells via engagement of their T-cell receptor (TCR) with viral peptides in the context of major histocompatibility complex (MHC) class I molecules on the surface of virus-infected cells. Cytolytic granules are released from cytotoxic T cells, enter target cells through perforin pores, and release granzymes and granulysin that induce apoptosis. Alternatively, Fas ligand expressed on cytotoxic T cells can bind to the Fas on virus-infected cells and induce apoptosis. mRNA, messenger RNA.

disseminated infections with environmental mycobacteria. These patients have increased susceptibility to severe infections with herpesviruses and certain respiratory viruses [35, 36]. Signal transducer and activator of transcription 1 (STAT1) mutations result in failure of type I IFNs to induce expression of IFN-inducible genes [37]. Two patients with autosomal recessive STAT1 mutations had disseminated Bacille Calmette-Guérin (BCG) disease and died with disseminated viral infections. IFN- α and IFN- β failed to inhibit virus replication in cells derived from each child. An additional patient with partial STAT1 deficiency with impaired (but not absent) IFN- α and IFN- β signaling had severe CMV and VZV infections [38].

Tyrosine kinase 2 deficiency, due to a homozygous mutation, was reported in a 22-year-old boy with an original diagnosis of hyperimmunoglobulin E syndrome. Manifestations of this syndrome include recurrent staphylococcal abscesses and respiratory tract infections and markedly elevated serum immunoglobulin

(Ig) E concentrations (>2000 IU/mL) [39]. However, the patient also experienced recurrent cutaneous viral infections, BCG lymphadenitis, and disseminated salmonella bacteremia (Table 2). Evaluation of immune responses in this patient revealed defects in IL-12 and IFN- α/β signaling (Figure 1), describing a new primary immunodeficiency.

Viral Infections Associated With the Prototypic Primary Immunodeficiencies

Patients with severe combined immunodeficiency syndromes can present with fatal viral infections (eg, herpesviruses, respiratory viruses, gastrointestinal viruses) that cause mild disease in other children. Vaccination with live attenuated virus vaccines or BCG can result in fatal infection. In addition, infections with bacterial pathogens, fungi, and *Pneumocystis* can be severe, recurrent, and fatal. These syndromes are characterized by severe defects in antibody and cell-mediated immunity and multiple gene defects [40]. NK cells are absent in 30%–50% of patients, making them more susceptible to severe viral diseases.

Common variable immunodeficiency (CVID) is the most common severe antibody deficiency affecting children and adults [41]. The hallmark of the disease is failure of B-cell differentiation with impaired secretion of immunoglobulins; hence, the most common infections observed in the majority of patients with CVID are recurrent, bacterial sinopulmonary infections. In addition, deficits in T-cell function have been identified in these patients, and CMV viremia and colitis have been reported [42]. Some patients with CVID have developed echovirus meningoencephalitis.

Miscellaneous Syndromes

Patients with dedicator of cytokinesis 8 (DOCK8) deficiency, previously classified as an atypical hyper-IgE syndrome, present with sinopulmonary infections, *Staphylococcus aureus* skin infections, and persistent, mutilating, recurrent cutaneous viral infections caused by HSV, VZV, molluscum contagiosum virus, or HPV (Table 2; Figure 3) [43, 44]. These viral infections often occur concurrently and frequently are unresponsive to therapy. Although the precise mechanism of DOCK8 in immune function remains to be defined, initial findings suggest a role in T-cell activation and proliferation [44].

Patients with idiopathic CD4⁺ lymphocytopenia are human immunodeficiency virus negative and present with a variety of opportunistic infections, including diffuse, persistent genital and cutaneous HPV infection, persistent and relapsing herpes zoster, EBV lymphoproliferative disease, and progressive multifocal leukoencephalopathy (Figure 3; Table 2) [45].

Patients with the autosomal dominant monocytopenia syndrome present with disseminated, recalcitrant cutaneous and genital papillomavirus infections and with disseminated non-tuberculous mycobacterial and fungal infections [46]. Other severe viral infections encountered are caused by HSV, VZV,

Table 2. Primary Immunodeficiencies Predisposing to Severe Diseases Associated With Various Viruses and Other Microbes

Viral infection or disease [references]	Mutated gene(s)/ protein	Immunodeficiency or syndrome	Other microbes	Associated clinical features	Immunologic findings
EBV, CMV, HSV, VZV, parvovirus B19, adenovirus [24]	<i>PRF1</i> /perforin 1; <i>MUNC13-4</i> /Munc; <i>STX11</i> /syntaxin 11; <i>STXBP2</i> /syntaxin binding protein 2	Familial hemophagocytic lymphohistiocytosis syndrome	Family history of disease; first episode can occur at any age	Fevers; splenomegaly; cytopenias; hemophagocytosis; decreased fibrinogen, increased triglycerides; increased ferritin; increased soluble IL-2R α	Low or absent NK-cell function; normal NK-cell number (CD56 ⁺ /CD16 ⁺); NK-cell and CD8 ⁺ T-cell cytotoxicity severely impaired; infiltration of organs by activated macrophages and CD8 ⁺ T cells
CMV, VZV, HSV [27]	Unknown	Absolute NK-cell deficiency ^a	<i>Mycobacterium avium-intracellulare</i> ; <i>Salmonella</i>	None	Absent or low NK-cell numbers (all CD56 ⁺ cells); absent or severely decreased NK-cell cytotoxicity
HPV [28]	Unknown	Classic NK-cell deficiency ^a	<i>Trychophyton</i>	None	Absent or low CD56 ⁺ /CD3 ⁻ cell numbers but CD56 ⁺ /CD3 ⁺ cells (NKT cells) present; absent or severely decreased NK-cell cytotoxicity
HSV, VZV, EBV, respiratory viruses [29]	<i>FCGR3A</i> (CD16)/low affinity receptor IIIa for Fc fragment of IgG or unknown gene	Functional NK-cell deficiency ^a	Not described	None	NK cells present; absent or severely decreased NK-cell cytotoxicity
CMV, HSV-1 (including HSE), HPV (disseminated), molluscum contagiosum, adenovirus [33, 34]	<i>IKBKG</i> (inhibitor of NF- κ B kinase γ)/NEMO (NF- κ B essential modulator)	X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency	Severe pyogenic bacterial infections; severe nontuberculous mycobacterial infections	With or without ectodermal dysplasia: conical or absent teeth; fine, sparse hair; frontal bossing; abnormal thermal regulation, decreased eccrine sweat glands; with or without lymphedema and osteopetrosis	Decreased IgG, increased IgM or IgA; absent antibody responses to vaccines; decreased NK-cell cytotoxicity; deficient in vitro cytokine inflammatory responses; variable cellular responses to T-cell mitogens and recall antigens in vitro
HSV, VZV, CMV, RSV and parainfluenza virus, HHV-8 [35, 36]	<i>IFN-γR1</i> /IFN- γ receptor 1; <i>IFN-γR2</i> /IFN- γ receptor 2	IFN- γ receptor deficiency	Disseminated nontuberculous mycobacterial infection; disseminated BCG after vaccination; nontyphi <i>Salmonella</i> ; <i>Listeria</i> ; <i>Histoplasma</i>	None	Markedly increased serum IFN- γ level (>80 pg/mL; ELISA); normal results of standard screening for cellular and humoral immune function
HSV-1 (including HSE), molluscum contagiosum [37, 38]	<i>STAT1</i> /STAT1	Complete STAT1 deficiency	Disseminated nontuberculous mycobacterial infection; disseminated BCG after vaccination <i>Mycobacterium tuberculosis</i> nontyphi <i>Salmonella</i> ; <i>Listeria</i>	None	Normal cellular and humoral immune function; lack of cellular response to IFN- α/β and - γ

Table 2 continued.

Viral infection or disease [references]	Mutated gene(s)/ protein	Immunodeficiency or syndrome	Other microbes	Associated clinical features	Immunologic findings
HSV-1, molluscum contagiosum virus [39]	<i>TYK2</i> /tyrosine kinase 2	Tyrosine kinase 2 deficiency	Sinopulmonary infections; <i>Staphylococcus aureus</i> skin abscesses; oral candidiasis; BCG; nontyphi <i>Salmonella</i>	Atopic dermatitis	Impaired cellular responses to IFN- α/β ; impaired IFN- γ production due to impairment of IL-12 signaling; elevated serum IgE; normal T-, B-, and NK cell counts; neutrophils with normal function
RSV, influenza, parainfluenza virus 3, CMV, VZV, EBV, enterovirus, adenovirus, rotavirus, measles [40]	<i>IL2Rγ</i> /IL-2 receptor alpha chain (X-linked), <i>JAK3</i> / tyrosine protein kinase <i>JAK3</i> , <i>IL7Rα</i> /IL-7 receptor alpha chain, <i>RAG1</i> /V(D)J-recombination activating protein 1 <i>RAG2</i> /V(D)J-recombination activating protein 2, <i>DCLRE1C</i> /artemis, <i>ADA</i> /adenosine deaminase (accounting for ~85% of gene defects)	Severe combined immunodeficiency	Recurrent, persistent, and severe bacterial and fungal infections; <i>Pneumocystis jirovecii</i> ; <i>Candida</i> species; oral polio, BCG, or MMR vaccines may cause severe disease	Lymphoid tissue may be absent (tonsils, lymph nodes); with or without absent thymic shadow on chest radiographs; thrush; chronic diarrhea, failure to thrive, rashes	Severe age-adjusted lymphopenia absent or profoundly decreased T-cell proliferation to mitogens and antigens; panhypogammaglobulinemia; specific antibody responses severely impaired; absent NK cells in 30%–50% of cases
VZV, CMV, enterovirus (echovirus) [41, 42]	<i>ICOS</i> /inducible T-cell costimulator; <i>TNFRSF13B</i> /tum-or necrosis factor receptor superfamily 13B; <i>CD19</i> ^b	Common variable immunodeficiency disorders ^b	Recurrent sinopulmonary infections (encapsulated bacteria, <i>Mycoplasma</i>); <i>Giardia</i> ; cryptosporidium	Splenomegaly; lymphadenopathy; chronic diarrhea; granulomatous disease; autoimmune disease (eg, inflammatory bowel disease, rheumatoid-like arthritis, hemolytic anemia, thrombocytopenia); nonmalignant lymphoproliferative disease	Hypogammaglobulinemia; impaired functional antibody responses; impaired lymphocyte proliferation (20%); with or without decreased CD4 ⁺ T-cell counts; increased CD8 ⁺ T-cell counts with or without decreased NK cells; normal or decreased B-cell number; variably decreased T-cell function
HSV, VZV, molluscum contagiosum virus, HPV, PML [43, 44]	<i>DOCK8</i> /DOCK8	DOCK8 deficiency	<i>S. aureus</i> soft-tissue infections; mucocutaneous candidiasis; recurrent respiratory tract infections; <i>P. jirovecii</i> ; <i>Histoplasma</i> ; <i>Cryptococcus</i> ; <i>Listeria</i> , <i>Salmonella</i> , <i>Giardia</i>	Severe atopy: extensive food and environmental allergies, asthma; skin cancer; lymphoma; autoimmune hemolytic anemia; central nervous system vasculitis	Increased IgE levels; hypereosinophilia; with or without increased IgG and decreased IgM levels; normal, or decreased IgA levels; variable antibody responses to protein and polysaccharide antigens; with or without low CD4 ⁺ and CD8 ⁺ T- and B-cell and low NK cell counts; failure of T-cell proliferation
VZV, EBV CMV, HHV-8, HPV, molluscum contagiosum, JC virus [45]	Unknown	Idiopathic CD4 ⁺ lymphocytopenia	<i>P. jirovecii</i> ; disseminated TB; <i>Histoplasma</i> ; <i>Cryptococcus</i> ; <i>Candida</i> species	None	CD4 ⁺ T-cell count < 300 cells/mm ³ ; some with low CD8 ⁺ T-cell counts; immunoglobulin levels normal or slightly low

Table 2 continued.

Viral infection or disease [references]	Mutated gene(s)/ protein	Immunodeficiency or syndrome	Other microbes	Associated clinical features	Immunologic findings
HPV, severe, disseminated HSV, VZV, EBV, parvovirus B19 [46, 47]	<i>GATA2</i> /GATA binding protein 2	Autosomal dominant monocytopenia (monoMAC)	Nontuberculous mycobacteria; disseminated histoplasmosis; invasive aspergillosis; cryptococcal meningitis	Myelodysplasia and malignancies; pulmonary alveolar proteinosis; autoimmune diseases	Profound monocytopenia; B lymphocytopenia; normal immunoglobulin levels; NK lymphocytopenia; with or without T-cell lymphopenia
CMV, VZV, HSV, molluscum contagiosum virus, HPV [30]	<i>WAS</i> /WASP	Wiskott–Aldrich syndrome	Sinopulmonary infections with encapsulated bacteria; <i>P. jirovecii</i>	Thrombocytopenia; small platelet volume; eczema; autoimmune diseases; EBV-related B cell lymphoma	Moderate lymphopenia for both CD4 ⁺ and CD8 ⁺ T lymphocytes and, to a lesser extent, B lymphocytes; reduced invariant NKT cells; decreased lymphocyte proliferation in 50% of patients; low isohemagglutinin titers; normal IgG, decreased IgM, and increased IgA and IgE levels; decreased antibody responses to polysaccharide antigens

Abbreviations: BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; DOK8, dedicator of cytokinesis 8; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; *FCGR3A*, Fc gamma receptor IIIa.; HHV-8, human herpesvirus 8; HPV, human papillomavirus; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MMR, measles, mumps, and rubella; NF, nuclear factor; NK, natural killer; NKT, natural killer T; PML, progressive multifocal leukoencephalopathy; RSV, respiratory syncytial virus; STAT1, signal transducer and activator of transcription 1; VZV, varicella-zoster virus; *JAK3*, Janus kinase 3; *DCLRE1C*, DNA cross-link repair 1C.

^a NK cells can migrate out of the blood into the tissues and give a falsely low NK cell number and/or activity in the peripheral blood. Therefore, a diagnosis of NK cell deficiency should be made only if the NK cell count and/or function is consistently depressed on ≥ 3 separate occasions and other causes of NK cell deficiency have been excluded.

^b Of patients with common variable immunodeficiency, 75% have no identified genetic defect.

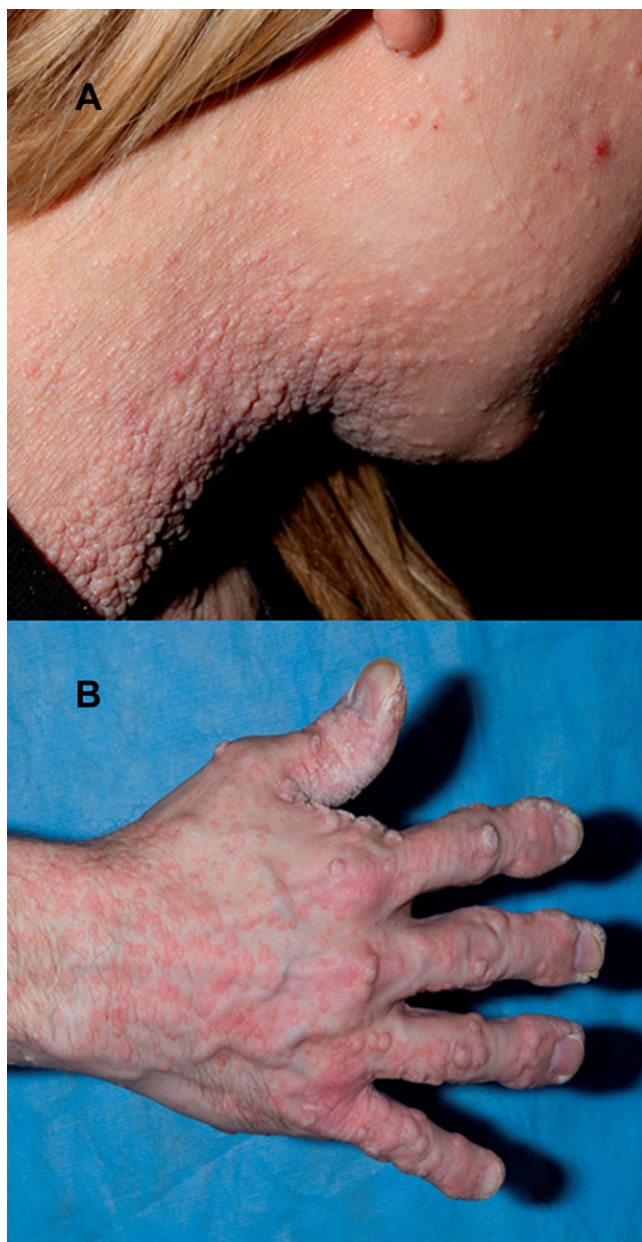


Figure 3. A, Disseminated molluscum contagiosum in a patient with deficiency of cytokines 8 deficiency. B, Cutaneous warts in a patient with idiopathic CD4⁺ lymphocytopenia.

EBV, and parvovirus B19. Patients have low numbers of monocytes, B cells, and NK cells. Recently, mutations in the gene *GATA2* were associated with this syndrome, also known as monoMAC [47].

Evaluation of a Patient With Suspected Primary Immunodeficiency Associated With Severe Viral Infections

The initial evaluation of a patient with suspected primary immunodeficiency is guided by the clinical presentation. The types of infections encountered guide the clinician to evaluate the patient for certain quantitative and functional defects. For

Historical characteristics suggestive of a primary immunodeficiency:

- Recurrent or persistent infections, especially with onset in childhood
- Severe infections caused by viruses (± other pathogens) that are usually not highly virulent
- Low blood cell counts or persistently high counts



Additional historical clues suggestive of a primary immunodeficiency:

- Vaccination complications
- Family history (childhood deaths or severe illnesses, consanguinity, multiple family members with autoimmune disease or malignancies)
- Autoimmune or allergic conditions (e.g. autoimmune endocrine disorders, rheumatic conditions, autoimmune hemolytic anemia, neutropenia or thrombocytopenia)
- Absence of immunosuppressive medications
- Culture or PCR results to confirm past and current infections



Physical examination especially of skin, tonsils, ears, lymph nodes, liver, and spleen



General immunologic work-up (screening tests):

- CBC with manual differential
- HIV test
- Quantitative serum immunoglobulin levels: IgG, IgA, IgM, and IgE
- Lymphocyte subset analysis, including B and T cells (CD4, CD8), NK and NKT cells by flow cytometry



Obtain specialized tests based on clinical presentation (refer to Tables 1 and 2):

- Antibody response to booster immunization if a humoral immunodeficiency is suspected
- In vitro lymphocyte proliferation responses to mitogen and antigen stimulation, if a cellular immunodeficiency is suspected
- NK cell cytotoxicity assays, if a defect in the innate immune system is suspected
- TLR signaling assays, if a defect in the innate immune response is suspected



Disease specific-evaluation (see Tables 1 and 2):

- Evaluation of expression of a mutated protein by Western blot or
- DNA sequencing to detect a gene mutation

Figure 4. Algorithm for the clinical evaluation of patients with suspected primary immunodeficiency associated with severe viral infections. Abbreviations: CBC, complete blood cell count; HIV, human immunodeficiency virus; Ig, immunoglobulin; NK, natural killer; NKT, natural killer T; PCR, polymerase chain reaction; TLR, Toll-like receptor.

example, a patient with viral infections and recurrent sino-pulmonary bacterial infections with encapsulated organisms should be evaluated for an antibody deficiency, whereas a patient with viral and disseminated nontuberculous mycobacterial infections should be evaluated for a defect in the IFN pathways. After a thorough history and physical examination focusing on aspects relevant to immunodeficiencies, screening tests should be performed (Figure 4). Depending on these results, advanced testing can be performed to further define the identified immune defect [48]. Consultation with an expert in primary immunodeficiency diseases should be sought to establish an accurate diagnosis and help determine the most effective therapy.

CONCLUSIONS

Evaluation of patients with severe viral infections suspected of having a primary genetic immunodeficiency has enhanced our

understanding of the important role of specific proteins in the immune system for protection from these infections [49]. The importance of the innate immune system has been demonstrated by the recent identification of mutations in various proteins in the IFN pathway that correlate with an increased susceptibility to viral infections, most notably herpesviruses [31]. The importance of NK cells in defense against viral infections is demonstrated by selective NK-cell deficiency syndromes. Impaired killing by cytotoxic T cells has long been associated with severe viral infections. Further study of the innate and adaptive immune systems will reveal the importance of other proteins in the control of severe viral infections. Thus, viruses continue to teach us about the intricacies of the immune system, and we have much more to learn.

Notes

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Since this paper was accepted, the MagT1 gene (a magnesium transporter protein) was reported to cause a T-cell immunodeficiency syndrome associated with severe Epstein-Barr virus infection (Li FY, Chaigne-Delalande B, Kanellopoulou C, et al. Second messenger role for Mg²⁺ revealed by human T-cell immunodeficiency. *Nature*. 2011; 475:471–6).

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